ORIGINAL ARTICLE INFECTIOUS DISEASES

De-escalation therapy among bacteraemic patients with community-acquired pneumonia

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Abstract

There is no evidence supporting the use of de-escalation therapy (DET) among patients with community-acquired pneumonia (CAP). We assessed the outcomes associated with DET among bacteraemic CAP patients. We performed a secondary analysis of the Community-Acquired Pneumonia Organization database, which contains data on 660 bacteraemic patients hospitalized because of CAP in 35 countries (2001–2013). Exclusion criteria were death within 72 h from admission and an inappropriate empirical antibiotic regimen. DET was defined as changing an appropriate empirical broad-spectrum regimen to a narrower-spectrum regimen according to culture results within 7 days from hospital admission. Two study groups were identified: patients whose antibiotic therapy was de-escalated (the DET group), and patients whose antibiotic therapy was not de-escalated (the N-DET group). The primary study outcome was 30-day mortality. Two hundred and sixty-one bacteraemic CAP patients were included. Gram-positive bacteria were responsible for 88.1% of the cases (*Streptococcus pneumoniae*, 75.9%). Gram-negative bacteria were responsible for for 7.3% of the cases. DET was performed in 165 patients (63.2%). The N-DET group was characterized by a more severe presentation at admission. After adjustment for confounders, DET was not associated with an increased risk of 30-day mortality. DET seems to be safe among bacteraemic patients with CAP. Randomized clinical trials are warranted to further explore these findings.

Keywords: Bacteraemia, broad-spectrum antibiotic treatment, community-acquired pneumonia, de-escalation, sepsis
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Introduction

Pneumonia is a predominant cause of sepsis, severe sepsis, and septic shock [1]. Mortality rates among patients with community-acquired pneumonia (CAP) range from 1% to 17.5% [2]. Empirical broad-spectrum antimicrobial treatment is aimed at achieving adequate antimicrobial coverage, and thus reducing mortality [3]. However, there is a risk that empirical broad-spectrum antimicrobial treatment can expose patients to overuse of antimicrobials and increase the resistance of microorganisms to treatment [4]. De-escalation has been proposed as a strategy to replace initial empirical broad-spectrum antimicrobial treatment with narrower-spectrum antimicrobial therapy [5]. This is done by either changing the pharmacological agent or discontinuing a pharmacological combination according to the patient's microbial culture results.

To date, there is conflicting evidence as to whether de-escalation of antimicrobial agents is effective and safe for adults with sepsis, severe sepsis, and septic shock [6–12]. Therefore, it is not possible to either recommend or not recommend the de-escalation of antimicrobial agents in clinical practice for bacteraemic patients with CAP [13].

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The aim of this study was to evaluate de-escalation therapy (DET) and its impact on clinical outcomes in bacteraemic patients hospitalized with CAP.

Materials and methods

Study design

Secondary analysis was restricted to bacteraemic patients included in the Community-Acquired Pneumonia Organization (CAPO) database. The CAPO database contains retrospective data on 660 bacteraemic adult patients with CAP hospitalized during the period 2001–2013 in 35 countries. The study protocol and data collection form are available at the study website (www.caposite.com). This study was conducted in accordance with the amended Declaration of Helsinki. The local institutional review board approved the protocol (University of Louisville Human Subjects Protection Program, IRB approval number 11.0613) [14].

Study population

Patients included in the study were aged ≥18 years and were characterized by the identification of bacteria likely to be the causative agents of pneumonia on blood cultures performed at hospital admission. Exclusion criteria included the following: (a) a single blood culture yielding coagulase-negative staphylococci, *Bacillus* species, *Corynebacterium* species, *Propionibacterium* species, and *Micrococcus* species [15]; (b) an inappropriate empirical broad-spectrum antibiotic regimen; and (c) death within 72 h from hospital admission, before de-escalation could have been instituted.

Study definitions

CAP was defined as a new pulmonary infiltrate (within 24 h from admission), associated with at least one of the following factors: a new or increased cough, an abnormal temperature (<35.8°C or >37.8°C), or an abnormal leukocyte count [16]. Pneumonia was considered as community-acquired if a patient had no history of hospitalization during the 2 weeks prior to admission. Severe sepsis was defined as the presence of at least one of the following signs of organ hypoperfusion or organ dysfunction on admission: (a) sepsis-induced hypotension, (b) a lactate level of >2 mmol/L, (c) urine output of <0.5 mL/kg/h for >2 h, (d) a creatinine level of >2.0 mg/dL, (e) a bilirubin level of >2 mg/dL, (f) a platelet count of <100 000 cells/L, or (g) coagulopathy (international normalized ratio of >1.5) [17]. DET was defined as changing an initially appropriate antimicrobial therapy from an empirical broad-spectrum regimen to a narrower-spectrum regimen (either by changing the antimicrobial agent or by discontinuing an eventual antimicrobial combination, or both) according to the microbial culture results within 7 days from hospital admission [18–20]. The empirical broad-spectrum antibiotic regimen was based on internationally approved guidelines for CAP (American Thoracic Society and the European Respiratory Society guidelines), and the following regimens were considered to be initial empirical broad-spectrum antibiotic regimens: (a) a β-lactam plus a macrolide, (b) a β-lactam plus a fluoroquinolone, (c) a fluoroquinolone plus aztreonam, (d) an aminopenicillin/β-lactamase inhibitor or antipseudomonal β-lactam, (e) an antipseudomonal β-lactam plus a fluoroquinolone, (f) an antipseudomonal β-lactam plus an aminoglycoside and a macrolide, (g) vancomycin or linezolid added to regimen (e) or (f), and (h) a β-lactam plus clindamycin or metronidazole [21,22]. An empirical broad-spectrum antibiotic regimen was considered to be appropriate when it was characterized by *in vitro*-demonstrated or presumed (for *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Legionella pneumophila*) activity against the causative microorganism. Multidrug resistance: among Gram-positive bacteria, methicillin-resistant *Staphylococcus aureus* was considered to be multidrug resistant, and the following Gram-negative pathogens were considered to be multidrug resistant: (a) *Enterobacteriaceae* producing extended-spectrum β-lactamase or carbapenemases; (b) *Pseudomonas aeruginosa* resistant to antipseudomonal penicillins, cephalosporins, carbapenems, and quinolones; (c) *Stenotrophomonas maltophilia*; and (d) *Acinetobacter baumanii* resistant to cephalosporins, carbapenems, and aminoglycoside [23,24]. Time to clinical stability (TCS) was defined according to the American Thoracic Society 2001 criteria for switching therapy from intravenous to oral antibiotic therapy [25]. Specifically, TCS was calculated as the number of days from the date of admission to the date when the patient met clinical stability criteria. Clinical stability was defined as follows: improved clinical signs (improved cough and shortness of breath), lack of fever for ≥8 h, improving leukocytosis (decreased by ≥10% from the previous day), and tolerating oral intake. The criteria for clinical stability were evaluated daily during hospitalization.

Study groups and outcomes

Among the entire study population, two groups of patients were identified according to the presence of DET: patients whose antibiotic therapy was de-escalated (DET group), and patients whose antibiotic therapy was not de-escalated (N-DET group).

Clinical failure during hospitalization, 30-day mortality and length of stay (LOS) in the hospital were the study outcomes. Clinical failure was defined by the occurrence of one of the following events: (a) acute pulmonary deterioration with the need for mechanical ventilation, (b) acute haemodynamic deterioration, or (c) in-hospital death up to 28 days after hospital admission [26]. Thirty-day mortality was defined as death from

any cause within 30 days from hospital admission. LOS was calculated among patients alive at discharge as the number of days from the date of admission to the date of discharge.

Study objectives

The primary objective of the study was to compare the 30-day mortality rate among patients whose antibiotic therapy was de-escalated (DET group) and patients whose antibiotic therapy was not de-escalated (N-DET group). Secondary objectives of the study included the following: (a) to compare clinical failure rates (DET group vs. N-DET group), (b) to compare 30-day mortality rates and clinical failure rates in the setting of severe sepsis (DET group vs. N-DET group), and (c) to compare 30-day mortality rates and clinical failure rates in the setting of monomicrobial *Streptococcus pneumoniae* infections (DET group vs. N-DET group).

Statistical analysis

Clinical outcomes were compared between the two study groups. A subgroup analysis in patients with severe sepsis and in those with monomicrobial *S. pneumoniae* infections was also performed. Continuous variables are presented as medians with interquartile ranges (IQRs). Categorical variables are presented as frequencies and percentages of the specified group. Comparisons between groups were performed with the Fisher exact test or the Kruskal–Wallis test as appropriate.

As DET may simply be a marker of early clinical improvement and not be causally associated with the outcomes under study, multivariable modelling was conducted to adjust for confounding effects in the relationships between DET and 30-day mortality, and between DET and clinical failure. To evaluate the adjusted association between DET and the outcomes (30-day mortality and clinical failure), a Poisson regression model was used. This model was chosen to calculate the adjusted risk ratio (RR) between the predictor and outcome. Poisson models are traditionally used for outcomes consisting of count data, and often suffer from issues associated with overdispersion. To correct for this and appropriately use this model in the situation of a binary outcome, we used a modified Poisson regression model with robust error variance [27]. In this model, we adjusted for the following variables: Pneumonia Severity Index, empirical antimicrobial therapy including a macrolide, need for intensive-care unit (ICU) admission or transfer, and severe sepsis. Model fit was evaluated with the Hosmer–Lemeshow goodness-of-fit test. p-Values of ≤ 0.05 were considered to be statistically significant in all analyses. For analysis, we used SAS enterprise guide v5.1 (SAS Institute, Cary, NC, USA) and R v3.1.2 (R Foundation for Statistical Computing, Vienna, Austria). The following R packages were used: sandwich [28] and rms [29].

Results

Study population

Complete microbiological therapeutic and outcome data were available for 414 of the 660 bacteraemic patients included in CAPO database. Of these, the following were excluded from our analysis: bacteraemia due to pathogens not consistent with CAP (single blood culture positive for coagulase-negative staphylococci, n = 13), inappropriate initial empirical broad-spectrum antibiotic regimen (n = 78), and death within 72 h from hospital admission (n = 34). Among those patients whose therapy was de-escalated, 28 were excluded from the study because DET occurred after $\geq$8 days from hospital admission. Thus, there were 261 evaluable subjects (Fig. 1): 96 in the N-DET group (36.8%), and 165 in the DET group (63.2%).

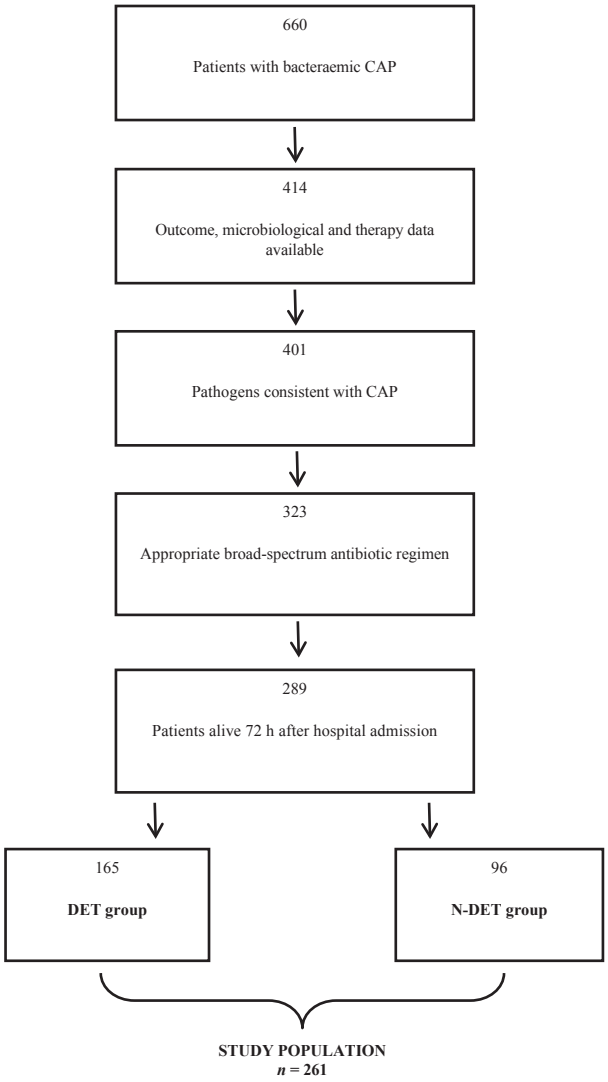

FIG. 1. Study population.

Baseline data

The median time from initiation of empirical antibiotic therapy to de-escalation was 3.0 days (IQR 3.0–5.0 days), and the median time from clinical stability to de-escalation was −1.0 days (IQR −4.0 to 1.0 days). Baseline demographics and comorbidities of the study population are summarized in Table 1, according to the two study groups. Despite a similar distribution of Pneumonia Severity Index Risk Classes IV–V, the clinical presentation at admission was more severe among patients in the N-DET group. This was shown by TCS. The median TCS in the study population was 6.0 days (IQR 3.0–8.0 days), with a significant difference between the N-DET group and the DET group (8.0 days (IQR 4.0–8.0 days) vs. 5.0 days (IQR 3.0–8.0 days), respectively, p < 0.01). The median duration of antibiotic therapy in the study population was 12 days (IQR 8–15 days). The duration of treatment was longer among patients in the DET group (13 days (IQR 9–16 days) vs. 10.5 days (IQR 7–14 days), respectively, p < 0.01] (Table 1). The vast majority of the infections were due to Gram-positive bacteria in both groups (86.1% and 91.7% in the DET group and the N-DET group, respectively). Overall, Gram-negative infections and mixed infections accounted for 7.3% and 4.6% of the cases, respectively. *S. pneumoniae* was the most frequently isolated pathogen (75.9%). Non-fermenters (*Pseudomonas* species, *n* = 3; *Moraxella catarrhalis*, *n* = 4; *Acinetobacter baumanii*, *n* = 1; *Stenotrophomonas maltophilia*, *n* = 1) and *Enterobacteriaceae* (*Escherichia coli*, *n* = 4; *Klebsiella* species, *n* = 4; *Citrobacter* species, *n* = 1; *Enterobacter* species, *n* = 1; *Proteus* species, *n* = 1) were the leading pathogens among Gram-negative bacteria. Multidrug-resistant organisms were

TABLE 1. Baseline demographics, comorbidities, disease severity, clinical, and laboratory findings on admission, microbiology, antibiotic data, and outcome information of the study population, according to the two study groups

	N-DET group (*n* = 96)	DET group (*n* = 165)	p
Demographic data			
Age (years), median (IQR)	59.5 (44.0–77.5)	54.0 (40.0–71.0)	**0.03**
Male sex, *n* (%)	62/96 (64.6)	94/165 (56.9)	0.22
Comorbidities, *n* (%)			
Neoplastic disease	11/96 (11.5)	15/165 (9.1)	0.54
Chronic heart failure	10/96 (10.4)	21/165 (12.7)	0.58
Cerebrovascular disease	10/96 (10.4)	12/165 (7.3)	0.38
Renal disease	12/96 (12.5)	14/165 (8.5)	0.30
Liver disease	8/96 (8.3)	20/165 (12.1)	0.34
Neurological disease	14/96 (14.6)	8/165 (4.9)	**<0.01**
Diabetes mellitus	18/96 (18.8)	32/165 (19.4)	0.89
Chronic obstructive pulmonary disease	12/96 (12.5)	22/165 (13.3)	0.85
HIV infection	8/96 (8.3)	30/165 (18.2)	**0.03**
Nursing home resident	7/47 (14.9)	11/88 (12.5)	0.70
Severity indicators			
Admission to ICU at hospital arrival, *n* (%)	31/96 (32.3)	36/165 (21.8)	0.06
Transfer to ICU during hospital stay, *n* (%)	5/70 (7.1)	13/124 (10.5)	0.44
PSI class IV–V, *n* (%)	59/96 (61.5)	89/165 (53.9)	0.24
Heart rate (beats/min), median (IQR)	107.5 (94.0–120.0)	110.0 (99.0–125.0)	0.18
Respiratory rate (breaths/min), median (IQR)	26.5 (20.0–32.0)	24.0 (20.0–28.0)	0.19
White blood cell count, cell × $10^3/mm^3$, median (IQR)	13.0 (9.9–21.0)	15.0 (9.0–19.6)	0.89
Systolic blood pressure (mmHg), median (IQR)	108.5 (93.5–130.0)	116.0 (101.5–134.5)	0.07
Severe sepsis, *n* (%)	49/96 (51.0)	65/165 (39.4)	0.07
Microbiology, *n* (%)			
Gram-positive infections	88/96 (91.7)	142/165 (86.1)	0.18
Gram-negative infections	4/96 (4.2)	15/165 (9.1)	0.14
Mixed infections	4/96 (4.2)	8/165 (4.8)	1.00
Multidrug-resistant pathogen	5/96 (5.2)	11/165 (6.7)	0.63
Management and clinical progression, median (IQR)			
Time from arrival to antibiotic therapy (h)	3.5 (2.0–6.2)	4.0 (2.0–6.0)	0.56
Time from diagnosis to antibiotic therapy (h)	1.0 (0.0–3.0)	1.0 (0.0–2.5)	0.94
Time from sample collection to DET (days)	NA	3.0 (3.0–5.0)	NA
Time from TCS to DET (days)	NA	−1.0 (−4.0 to 1.0)	NA
TCS (days)	8.0 (4.0–8.0)	5.0 (3.0–8.0)	**<0.01**
Duration of antibiotic therapy (days)	10.5 (7.0–14.0)	13.0 (9.0–16.0)	**<0.01**
Initial empirical broad-spectrum antibiotic regimen, *n* (%)			
β-Lactam plus a macrolide	44/96 (45.8)	86/165 (52.1)	0.33
β-Lactam plus a fluoroquinolone	25/96 (26.0)	27/165 (16.4)	0.06
β-Lactam plus clindamycin or metronidazole	2/96 (2.1)	6/165 (3.6)	0.71
Aminopenicillin/β-lactamase inhibitor or antipseudomonal β-lactam	6/96 (6.25)	4/165 (2.4)	0.18
Antipseudomonal β-lactam plus a fluoroquinolone	7/96 (7.3)	7/165 (4.2)	0.29
Antipseudomonal β-lactam plus an aminoglycoside and macrolide	0/96 (0.0)	1/165 (0.6)	1.00
Antipseudomonal β-lactam plus an aminoglycoside + macrolide or a fluoroquinolone plus vancomycin or linezolid	12/96 (12.5)	34/165 (20.6)	0.09
Clinical outcomes			
Length of hospital stay among patients alive at discharge (days), median (IQR)	9.0 (5.0–16.0)	8.0 (5.0–15.0)	0.64
Clinical failure, *n* (%)	27/66 (40.9)	28/104 (26.9)	0.06
30-day mortality, *n* (%)	24/96 (25.0)	25/165 (15.1)	**0.04**

Statistically significant p-values are in bold.
DET, de-escalation therapy; HIV, human immunodeficiency virus; ICU, intensive-care unit; IQR, interquartile range; NA, not applicable; PSI, Pneumonia Severity Index; TCS, time to clinical stability.

isolated in 6.1% of the cases (MRSA, *n* = 15; *Stenotrophomonas maltophilia*, *n* = 1) (Table 1). A β-lactam plus either a macrolide or a fluoroquinolone was the empirical treatment most frequently administered to patients in both the DET group and the N-DET group (Table 1).

30-day mortality

Among the entire study population, a total of 49 patients (18.8%) died within 30 days from hospital admission (Table 2). The characteristics of patients who died vs. those who survived are reported in Table 2. There was a significantly lower 30-day mortality rate in the DET group than in the N-DET group in univariate analysis (25 patients (15.1%) vs. 24 patients (25.0%), p 0.04) (Tables 1 and 2). After adjustment for confounders, DET was not associated with an increased risk of 30-day mortality (RR 0.78 (95% CI 0.47–1.27), p 0.32) (Table 3).

TABLE 3. Thirty-day mortality: multivariate analysis

	Risk ratio	95% CI	p
Model intercept	0.05	0.02–0.12	**<0.01**
De-escalation	0.78	0.47–1.27	0.32
Pneumonia Severity Index class IV–V	1.01	1.01–1.02	**<0.01**
Macrolide therapy	1.18	0.71–1.95	0.53
Need for intensive care	2.07	1.17–3.68	**0.01**
Severe sepsis	1.02	0.59–1.75	0.94

Statistically significant p-values are in bold.

Clinical failure

To assess the performance of DET, we analysed several other outcome metrics. Data on clinical failure were available for 170 patients. Among these patients, 55 (32.3%) experienced a clinical failure. A lower rate of clinical failure was detected in the DET group than in the N-DET group (28 patients (26.9%) vs. 27 patients (40.9%), p 0.06) (Tables 1 and 4). Similarly to what was found for the 30-day-mortality risk, the risk of clinical failure was not increased among those patients whose antibiotic therapy was de-escalated (RR 0.89 (95% CI 0.63–1.27), p 0.54) (Table 5). The median LOS among patients alive at discharge was 8 days (IQR 5–16 days). No difference in terms of LOS was

TABLE 2. Thirty-day mortality: univariate analysis

	Alive at day 30 (*n* = 212)	Died by day 30 (*n* = 49)	p
Demographic data			
Age (years), median (IQR)	54.5 (40.5–71.0)	58.0 (45.0–80.0)	0.06
Male sex, *n* (%)	126/212 (59.4)	30/49 (61.2)	0.82
Comorbidities, *n* (%)			
Neoplastic disease	21/212 (9.9)	5/49 (10.2)	1.00
Chronic heart failure	21/212 (9.9)	10/49 (20.4)	**0.04**
Cerebrovascular disease	10/212 (4.7)	12/49 (24.5)	**<0.01**
Renal disease	22/212 (10.4)	4/49 (8.2)	0.79
Liver disease	22/212 (10.4)	6/49 (12.2)	0.70
Neurological disease	13/212 (6.1)	9/49 (18.4)	**0.01**
Diabetes mellitus	40/212 (18.9)	10/49 (20.4)	0.80
Chronic obstructive pulmonary disease	24/212 (11.3)	10/49 (20.4)	0.09
HIV infection	30/212 (14.2)	8/49 (16.3)	0.70
Nursing home resident	10/102 (9.8)	8/33 (24.2)	**0.04**
Severity indicators			
Admission to ICU at hospital arrival, *n* (%)	44/212 (20.8)	23/49 (46.9)	**<0.01**
Transfer to ICU during hospital stay, *n* (%)	14/168 (8.3)	4/26 (15.4)	0.27
PSI score IV–V, *n* (%)	109/212 (51.4)	39/49 (79.6)	**<0.01**
Heart rate (beats/min), median (IQR)	110.0 (95.5–122.0)	114.0 (99.0–128.0)	0.34
Respiratory rate (breaths/min), median (IQR)	24.0 (20.0–30.0)	30.0 (20.0–40.0)	**0.03**
White blood cell count, cell × $10^3/mm^3$, median (IQR)	15.0 (9.9–22.7)	12.0 (4.0–15.0)	**<0.01**
Systolic blood pressure (mmHg), median (IQR)	115.0 (100.0–133.0)	101.5 (85.5–122.0)	0.05
Severe sepsis, *n* (%)	86/212 (40.6)	28/49 (57.1)	**0.03**
Microbiology, *n* (%)			
Gram-positive infections	188/212 (88.7)	42/49 (85.7)	0.56
Gram-negative infections	13/212 (6.1)	6/49 (12.2)	0.14
Polymicrobial infections	11/212 (5.2)	1/49 (2.0)	0.47
Multidrug-resistant pathogen	11/212 (5.2)	5/49 (10.2)	0.19
Management and clinical progression, median (IQR)			
Time from arrival to antibiotic therapy (h)	4.0 (2.0–6.0)	3.5 (2.0–7.0)	0.82
Time from diagnosis to antibiotic therapy (h)	1.0 (0.0–2.5)	1.0 (0.0–3.0)	0.74
Time from sample collection to DET (days)	3.0 (3.0–5.0)	3.0 (2.0–5.0)	0.76
Time from TCS to DET (days)	−1.0 (−4.0 to 1.0)	−3.0 (−5.0 to 2.0)	**<0.01**
TCS (days)	5.0 (2.0–8.0)	8.0 (8.0–8.0)	**<0.01**
Initial empirical broad-spectrum antibiotic regimen, *n* (%)			
β-Lactam plus a macrolide	109/212 (51.4)	21/49 (42.8)	0.28
β-Lactam plus a fluoroquinolone	45/212 (21.2)	7/49 (14.3)	0.27
β-Lactam plus clindamycin or metronidazole	7/212 (3.3)	1/49 (2.0)	1.00
Aminopenicillin/β-lactamase inhibitor or antipseudomonal β-lactam	9/212 (4.3)	1/49 (2.0)	0.69
Antipseudomonal β-lactam plus a fluoroquinolone	8/212 (3.8)	6/49 (12.2)	**0.03**
Antipseudomonal β-lactam plus an aminoglycoside and macrolide	1/212 (0.5)	0/49 (0.0)	1.00
Antipseudomonal β-lactam plus an aminoglycoside + macrolide or a fluoroquinolone plus vancomycin or linezolid	33/212 (15.6)	13/49 (26.5)	0.07
DET, *n* (%)	140/212 (66.0)	25/49 (51.0)	**0.04**

Statistically significant p-values are in bold.
DET, de-escalation therapy; HIV, human immunodeficiency virus; IQR, interquartile range; PSI, Pneumonia Severity Index; TCS, time to clinical stability.

TABLE 4. Clinical failure: univariate analysis

	Clinical success (n = 115)	Clinical failure (n = 55)	p
Demographic data			
Age (years), median (IQR)	56.0 (44.0–75.0)	55.0 (40.0–79.0)	0.89
Male sex, *n* (%)	65/115 (56.5)	29/55 (52.7)	0.64
Comorbidities, *n* (%)			
Neoplastic disease	13/115 (11.3)	3/55 (5.5)	0.22
Chronic heart failure	8/115 (6.9)	9/55 (16.3)	0.06
Cerebrovascular disease	6/115 (5.2)	12/55 (21.89	**<0.01**
Renal disease	13/115 (11.39	7/55 (12.7)	0.79
Liver disease	8/115 (6.9)	7/55 (12.7)	0.25
Neurological disease	8/115 (6.9)	12/55 (21.8)	**<0.01**
Diabetes mellitus	26/115 (22.6)	9/55 (16.4)	0.35
Chronic obstructive pulmonary disease	14/115 (12.2)	10/55 (18.2)	0.29
HIV infection	21/115 (18.3)	13/55 (23.6)	0.41
Nursing home resident	6/18 (33.3)	8/28 (28.6)	0.73
Severity indicators			
Admission to ICU at hospital arrival, *n* (%)	12/115 (10.4)	28/55 (50.9)	**<0.01**
Transfer to ICU during hospital stay, *n* (%)	3/115 (2.6)	11/45 (24.4)	**<0.01**
PSI score IV–V, *n* (%)	56/115 (48.7)	42/55 (76.4)	**<0.01**
Heart rate (beats/min), median (IQR)	110.0 (94.0–121.0)	112.5 (100.0–125.0)	0.13
Respiratory rate (breaths/min), median (IQR)	24.0 (20.0–30.0)	27.5 (21.0–35.5)	**0.01**
White blood cell count, cell × 10^3/mm^3, median (IQR)	15.1 (9.8–22.7)	12.6 (6.0–16.7)	**0.04**
Systolic blood pressure (mmHg), median (IQR)	116.0 (101.0–135.0)	105.0 (87.0–120.0)	**<0.01**
Severe sepsis, *n* (%)	53/115 (46.1)	44/55 (80.0)	**<0.01**
Microbiology, *n* (%)			
Gram-positive infections	107/115 (93.0)	46/55 (83.6)	0.06
Gram-negative infections	4/115 (3.5)	7/55 (12.7)	**0.02**
Polymicrobial infections	4/115 (3.5)	2/55 (3.6)	1.00
Multidrug-resistant pathogen	6/115 (5.2)	7/55 (12.7)	0.12
Management and clinical progression, median (IQR)			
Time from arrival to antibiotic therapy (h)	4.0 (2.0–6.0)	3.0 (1.5–6.0)	0.50
Time from diagnosis to antibiotic therapy (h)	1.0 (0.0–2.0)	0.5 (−0.5 to 2.5)	0.81
Time from sample collection to DET (days)	3.0 (3.0–5.0)	3.0 (2.0–4.5)	0.52
Time from TCS to DET (days)	−1.0 (−3.5 to 1.0)	−4.0 (−6.0 to 2.0)	**<0.01**
TCS (days)	4.0 (2.0–8.0)	8.0 (8.0–8.0)	**<0.01**
Initial empirical broad-spectrum antibiotic regimen, *n* (%)			
β-Lactam plus a macrolide	58/115 (50.4)	19/55 (34.5)	0.05
β-Lactam plus a fluoroquinolone	33/115 (28.7)	9/55 (16.4)	0.08
β-Lactam plus clindamycin or metronidazole	3/115 (2.6)	0/55 (0.0)	0.55
Aminopenicillin/β-lactamase inhibitor or antipseudomonal β-lactam	2/115 (1.7)	2/55 (3.6)	0.60
Antipseudomonal β-lactam plus a fluoroquinolone	1/115 (0.8)	5/55 (9.1)	**0.01**
Antipseudomonal β-lactam plus an aminoglycoside and macrolide	0/115 (0.0)	0/55 (0.0)	—
Antipseudomonal β-lactam plus an aminoglycoside + macrolide or a fluoroquinolone plus vancomycin or linezolid	18/115 (15.6)	20/55 (36.4)	**<0.01**
DET, *n* (%)	76/115 (66.1)	28/55 (50.9)	0.06

Statistically significant p-values are in bold.
DET, de-escalation therapy; HIV, human immunodeficiency virus; ICU, intensive-care unit; IQR, interquartile range; PSI, Pneumonia Severity Index; TCS, time to clinical stability.

detected between the DET group and the N-DET group (8 days (IQR 5–13.5 days) vs. 9 days (IQR 5–18 days), p 0.42).

Subgroup analyses

In a subgroup of patients with severe sepsis (n = 114), DET was performed in 65 cases (57.0%). The strategy of de-escalation was not associated with increased rates of adverse outcome among severe sepsis patients (30-day mortality rates in DET and N-DET subjects, 16.9% vs. 34.7%, respectively, p 0.03; clinical failure rates in DET and N-DET subjects, 40.0% vs. 52.4%, p 0.22). Among 198 patients with monomicrobial CAP due to *S. pneumoniae*, DET was not associated with higher rates of 30-day mortality and clinical failure (30-day mortality rates in DET and N-DET subjects, 9.7% vs. 23.6% respectively, p < 0.01; clinical failure rates in DET and N-DET subjects, 17.3% vs. 41.2%, p < 0.01).

TABLE 5. Clinical failure: multivariate analysis

	Risk ratio	95% CI	p
Model intercept	0.08	0.04–0.16	**<0.01**
De-escalation	0.89	0.63–1.27	0.54
Pneumonia Severity Index class IV–V	1.01	1.00–1.02	0.05
Macrolide therapy	0.97	0.66–1.43	0.89
Need for intensive care	4.08	2.39–6.97	**<0.01**
Severe sepsis	1.70	0.98–2.96	0.06

Statistically significant p-values are in bold.

Discussion

This study has demonstrated that DET is performed in almost two-thirds of the bacteraemic patients hospitalized with CAP, and that one of the main drivers for this is the patient's response during hospitalization. DET is not associated with an increased risk of either 30-day mortality or clinical failure during hospitalization. Furthermore, DET does not seem to lead to higher 30-day mortality and clinical failure rates when used in difficult clinical settings, such as in patients with severe sepsis.

In 2014, several studies evaluated the safety and the efficacy of DET [6–8,11,30]. Unfortunately, the results of these studies were divergent. In the observational study by Garnacho-Montero *et al.*, DET was associated with reduced risks of in-hospital mortality and 90-day mortality [7]. Mokart *et al.* evaluated the performance of DET in neutropenic patients with severe sepsis. DET did not modify the risk of death within the first 30 days or within 1 year after ICU discharge [8]. Although it was a secondary endpoint in the study by Koupetori *et al.*, DET was not associated with an increased risk of adverse outcomes among patients with Gram-negative bloodstream infection [30]. Cremers *et al.* found that de-escalating broad-spectrum antibiotic treatment to penicillin monotherapy was not associated with an increased risk of mortality in patients with pneumococcal bacteraemia. Moreover, they found that DET in pneumococcal pneumonia cases was associated with a decreased risk of mortality [11]. Leone *et al.* performed the first randomized trial on DET in severe sepsis. The authors showed that DET was inferior to continuation of the initial empirical antibiotic therapy in terms of length of ICU stay. This trial had some limitations: (a) the discontinuation of companion antibiotics (aminoglycoside, fluoroquinolone, or macrolide) was permitted by the study protocol in both the de-escalation group and the continuation group—as a consequence, some patients whose therapy was de-escalated were included in the continuation group; (b) the primary endpoint was time from study inclusion and ICU discharge—this is a surrogate endpoint, and it may have been severely affected by the number of patients who died during the ICU stay; and (c) the sample size of the study was small (n = 116) [6]. Owing to the above bias and limitations, the results of this trial should be analysed with caution.

Although not conclusive, the evidence provided by our study supports the use of DET for bacteraemic patients with CAP, in line with the results of other observational studies [7,8]. Moreover, our findings support the safety of DET in the setting of lung infections: by focusing on bacteraemic patients with CAP, we avoided heterogeneity biases. Kollef and Joung achieved similar results [31]. Finally, our study showed more extensive use of de-escalation than the rates (39–52%) reported in previous studies [9,10,32]. It is of note that this study showed a prolonged duration of the antibiotic treatment among bacteraemic patients with CAP (median duration: 12 days), and an even longer duration among those patients whose therapy was de-escalated. The optimal duration of antibiotic therapy among bacteraemic patients with CAP is still a matter of controversy, and no specific recommendations are currently available. As a result, clinicians probably overtreated patients. Why DET patients were treated for a significantly longer period than N-DET patients is difficult to explain. The results of the recently completed 'Duration Trial' (clinical trial: NCT01492387) will provide evidence to identify the optimal duration of therapy for bacteraemic patients with CAP.

This study has several noteworthy limitations. As this is a retrospective observational cohort study, we cannot make any definitive inference about the association between DET use and patient outcomes. Our study lacked detailed information about the adverse events associated with antibiotic therapy and about the follow-up period. Follow-up data would have been extremely important to estimate the recurrence of CAP, the rate of re-hospitalization, the causes of late mortality, and the development of drug resistance. The relatively small number of patients with severe sepsis limited our ability to detect significant differences between DET and N-DET patients in this clinical subset. Finally, we did not address other important questions regarding bacteraemic CAP, such as the effect on outcome of switching from intravenous to oral therapy.

In conclusion, our findings suggest that DET is not associated with adverse outcomes in the setting of bacteraemic patients presenting with CAP. Although non-definitive, the evidence generated by this study supports the design of prospective studies and randomized clinical trials to further evaluate the use of DET among bacteraemic patients with CAP.

Transparency declaration

The authors declare that they have no conflicts of interest.

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